Sequence Compliance:

The Examiner states that the application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, the Examiner also suggests that the application fails to fully comply with the requirements of 37 C.F.R. § 1.821 through 1.825. In particular, the Examiner notes that

(a) On page 14, two oligonucleotide primers are disclosed without benefit of SEQ ID NOs.

(b) On page 18, two different amino acid sequences are disclosed without benefit of SEQ ID NOs.

Applicants have amended the specification to include sequence identifiers for the noted sequences. These sequences were filed previously on April 25, 2001 with the corresponding sequence numbers in a sequence listing as set forth in 37 CFR 1.821. No new matter has been added.

Objections to the Specification:

This application is objected to because it does not contain an abstract of the disclosure as required by 37 C.F.R. §1.72(b). Applicants herein submit an abstract on a separate sheet.

The specification is objected to for having an unclear copy. On pages 2-4, the following are unclear by virtue of an illegible copy: formula I, R^1, formula III, and formula IV. Applicants herein submit substitute pages 2-4 of the specification with clear copy. See attached.

The specification is objected to for allegedly being confusing with respect to the sequence listing. The sequence listing contains 6 identified sequences, while SEQ ID NOs:1 and 2 are identified in the specification. Applicants have amended the specification to include sequence identifiers 3-6 with the appropriate sequences. These sequences were previously submitted with the sequence listing.

Claim Objections:

Claim 19 is objected to under 37 C.F.R. §1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner suggests that rewriting the claim to change the phrase "obtainable from *Streptomyces*" to

"native to *Streptomyces*" would place the claim in proper dependent form. Applicants have rewritten the claim based on the Examiner's suggestion.

Claim 23 is objected to under 37 C.F.R. §1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner alleges that the manner in which the polypeptide used in claims 15 and 16 is obtained does not further limit the claim. Applicants respectfully disagree. Applicants submit that the limitation of claim 23 reciting that the polypeptide is obtained from a recombinant vector is proper and therefore request reconsideration of this claim objection.

Claim Rejections:

35 U.S.C. §101

Claims 15-20 and 23 are rejected under 35 U.S.C. §101 because the claimed invention is directed to non-statutory subject matter. The Examiner alleges that claims 15-20 and 23, as written, do not sufficiently distinguish over processes as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed methods and the naturally occurring methods. The Examiner further alleges that in the absence of the "hand of man," the naturally occurring processes are considered non-statutory subject matter, and that the claims should be amended to indicate the hand of the inventor.

Applicants have amended claim 15 and 16 to include the term "isolated" with respect to a polypeptide having 95% sequence identity to SEQ ID NO:2. Applicants provide a definition of "isolated" as including "by the hand of man" in the specification. See page 9, lines 18-23 of the specification. In addition, Applicants also disclose in the specification that the polypeptide may be used in isolated form. See page 4, lines 19-21 and page 5, lines 26-28. As claims 17-20 and 23 depend from claims 15 and 16 as amended, rejection of these claims under 35 U.S.C. §101 is rendered moot.

35 U.S.C. §102

Claims 15-20 and 23 are rejected under 35 U.S.C. §102(b) as being anticipated by Baggaley, *et al.* (WO 94/12654) as evidenced by Jensen *et al.* (CA 2108113). The Examiner alleges that the claims are "drawn to methods of making formula IV (see Claim 16) by contacting SEQ ID NO:2, a 512 amino acid protein, with formula III (N^2-(2-carboxyethyl)-(S)-arginine)." In particular, the Examiner alleges that Baggaley, *et al.* "teach the biosynthetic

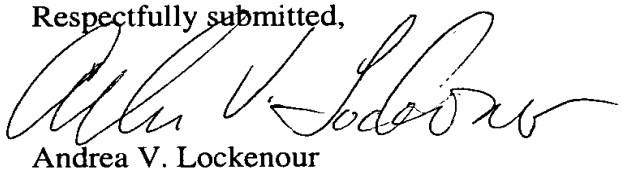
route producing clavulanic acid in *Streptomyces clavulegirus* (see page 1 and Figure 1). This route includes Applicants' formulas III and VI as shown in structure 'A' and 'B', respectively, in Figure 1 of Baggaley *et al.*" The Examiner also alleges that the enzyme SEQ ID NO:2 is presented by Jensen, *et al.*

Applicants respectfully traverse this rejection. A single prior art reference anticipates a claimed invention only if it identically shows every element of the claimed invention. *In re Bond*, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990). The Applicants respectfully submit that Baggaley, *et al.* cannot properly anticipate the claimed invention because this reference does not identically disclose the Applicants' methods for preparing Formulas (I) and (IV). Baggaley, *et al.* merely teach the conversion of Structure A by an enzyme. They do not teach an *isolated* enzyme having 95% sequence identity to SEQ ID NO:2.

Furthermore, Jensen, *et al.* disclose a deduced amino acid structure of SEQ ID NO:2. However, Jensen *et al.* do not provide a functional correlation of this polypeptide with the processes for the preparation of Formulas I or IV as disclosed by Applicants. Jensen, *et al.* merely teach the deduced amino acid sequence absent any disclosed function.

Applicants respectfully submit that the aforementioned amendments and remarks are fully responsive to the Office Action and request reconsideration of the rejections stated therein. The Examiner is invited to contact Applicants' undersigned at the telephone number provided below if such might facilitate allowance of the pending claims.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please

At page 14, lines 14-19, please add the following sequence identifiers to the text:

--5' primer:

Nde1

5' G GAA TCC *CAT ATG* GGG GCA CCG GTT CTT C 3' (SEQ ID NO:3)

3' primer:

BamH I

5' CGC *GGA TTC* CTA GGC CGC CCC CCG CG 3' (SEQ ID NO:4)

--

At page 18, lines 2 and 11, please add the following sequence identifiers to the text:

--raised against a 16 amino acid peptide corresponding to a region close to the C-terminus of the predicted orf3 protein (VGGGRHPSEVDTDDVC) (SEQ ID NO:5) (Canadian patent application no. 2108113) which gave a positive result for the 56 KDa protein corresponding to the predicted size of the orf3 protein.

From SDS-PAGE gel anaylsis of the protein fractions collected by this method it was estimated that the best fractions containing orf3 were ca. 40% pure.

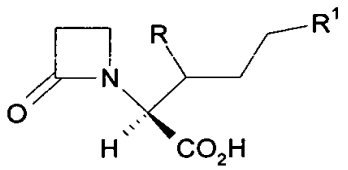
As a final confirmation of the orf3 protein N-terminal amino acid sequencing was undertaken using standard Edman degradation methodology. The sequence generated from this showed 100% sequence identity with the predicted sequence (Figure 12 in Canadian patent application no. 2108113), ie.

NH_2-GAPVLPAAFGFLASARTGGG (SEQ ID NO:6)--

In the Claims:

Please amend claims 15 and 16 as follows:

15. (Amended) A process for preparing compounds of formula (I)

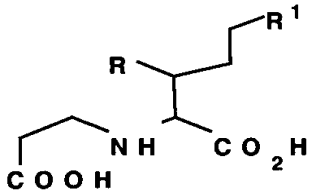


(I)

wherein R is H or OH and R^1 is

and where R^2 = H or C_{1-6} alkyl

by contacting a compound of formula (II)

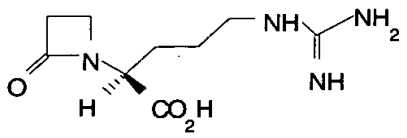


(II)

where the variables are as defined in formula (I)

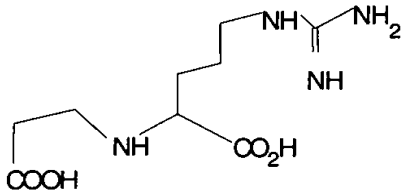
with an isolated polypeptide having at least 95% identity to the amino acid sequence of SEQ ID NO:2 over the entire length of SEQ ID NO:2, and having β-lactam synthetase activity.

16. (Amended) A process for preparing a compound of formula (IV)



(IV)

by contacting N^2-(2-carboxyethyl)-(S)-arginine; formula (III)



(III)

with an isolated polypeptide having at least 95% identity to the amino acid sequence of SEQ ID NO:2 over the entire length of SEQ ID NO:2, and having β-lactam synthetase activity.

19. (Amended) A process according to claim 15 or 16 wherein the polypeptide having β-lactam synthetase activity is native to[obtainable from] *Streptomyces* species.